PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB 791 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06745	26.06.2003	02.07.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K9/127		
Applicant		
ARCAMONE, Federico et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2004	02.11.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vermeulen, S Telephone No. +49 89 2399-7520

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06745

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 9
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2,3,5,8
	No:	Claims	1,4,6,7
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document/s/:

   D1: WO 01/35935 A (ONCOZYME PHARMA INC.) 25 May 2001
   D2: US-B-6 187 5721 (GOODRICH JR RAYMOND P ET AL) 13 February 2001
   D3: US 2002/037856 A1 (KHORLIN ALEXANDER ET AL) 28 March 2002
   D4: US-A-4 766 142 (ARCAMONE FEDERICO ET AL) 23 August 1988

2. The subject-matter of claims 1, 4, 6 and 7 is not considered to involve an inventive step (Art. 33(3) PCT) in view of prior art teaching which can be taken from D1.

2.1 The problem to be solved by the present application appears to be the provision of an improved formulation of antiinfective and antitumour agents belonging to the class of the lexitropsins which exhibits optimal pharmacological properties, i.e. optimal bio-availability, when used in topical or parenteral administration. This problem is solved according to the present application by formulation of the lexitropsins together with phospholipids, e.g. in form of liposomes, micelles, nanoparticles or phospholipid complexes.

2.2 The closest state of the art is document D1, which deals with pharmaceutical compositions comprising an inhibitor of endo-exonuclease activity for treating cancer. A known inhibitor of endo-exonuclease activity is distamycin A (cf. D1: page 8, line 14), which belongs to the class of lexitropsins as defined by the formula I and II of the present application. Although D1 does not disclose a specific example of distamycin associated with a phospholipid carrier, the document clearly teaches the benefits of such association in the field of tumour therapy. The association of the active agents disclosed in D1, i.e. including distamycin, with an excipient such as a micelle, a vesicle or a liposome is taught to facilitate transport of the active agents, improve their solubilization, improve their delivery to tumour cells and improve the interaction with tumour cells to make these cells more permeable to the active agents. Such teaching is found on page 9 (lines 18-24) and page 28 (lines 24-26). Accordingly, the skilled person looking for an improved formulation of distamycin would, upon reading D1, consider the association with a phospholipid as an obvious alternative to enhance the

pharmacological properties of e.g. a distamycin formulation. Hence, no inventive step can been seen in the subject-matter of claims 1 and 4. Claims 6 and 7 also do not involve an inventive step, since both topical and parenteral administration are taught by D1 (cf. page 28, lines 22-23).

3. The subject-matter of claims 2, 3, 5 and 8 is considered to meet the requirements of novelty and inventive step (Art. 33(2)(3) PCT).

3.1 The specific embodiments of claims 2 and 3 are not suggested by D1 or any of D2-D4. According to the present application these specific embodiments enable improved therapeutic efficacy of several compounds belonging to the class of lexitropsins in antitumour therapy, but also in antiviral and antibacterial therapies. This cannot obviously be derived from D1-D4.

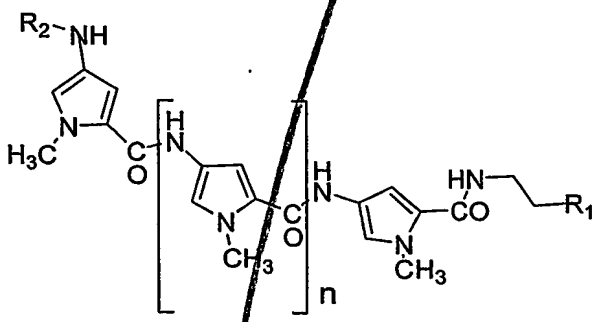
3.2 The state of the art according to D1-D4 furthermore does not suggest a phospholipidic preparation of the compound of formula X as defined in claim 5. According to the present application this compound, which has anti-malaria activity, shows enhanced therapeutic efficacy when formulated with a phospholipid excipient as defined in the claims. This is not derivable from the above cited prior art.

3.3 Similarly, none of the prior art documents discloses or suggests the subject-matter of claim 8. The teaching of D1 is directed to antitumour treatments and does not deal with the antiviral or antibacterial properties of lexitropsins. The document does not contain any indication which would incite the skilled person to formulate compounds belonging to the class of lexitropsins in combination with phospholipids in order to enhance antiviral and/or antibacterial activity of said compounds.

4. The subject-matter of claims 1-8 is considered to be industrially applicable and accordingly meets the requirements of Art.33(4) PCT.

CLAIMS

1. A phospholipidic preparation consisting in a release system and a lexitropsin of general formula I



I (n=0,1)

in which R_1 is a functional group, preferably a basic one such as a simple or substituted amidine, a secondary or tertiary amine, a quaternary ammonium group, a simple or substituted guanidine, examples of which, without limiting the present invention, may be

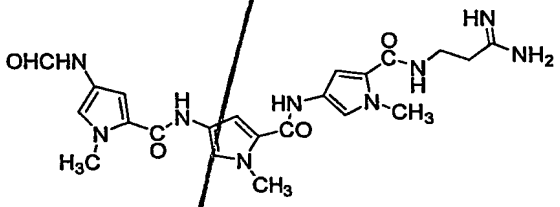
$-C(NH)NH_2$, $-C(NH)NHR_3$, $-NH_2$, NHR_3 $-N(R_3)_2$, $-NR_3R_4$, $-NH-C(NH)NH_2$, $-NH-C(NH)NHR_3$, $-N(CH_2)_4$, $-N(R_3)_3+$

whereas R_2 represents an aliphatic, aromatic, or arylaliphatic acylic group, also if substituted with atomic groups containing one or more heteroatoms such as atoms of oxygen, nitrogen, or R_2 represents a sequence of one or more residues of 1-methyl-4-aminopyrrole-2-carboxylic acid, acylated or not acylated at the N-terminus, also terminating with a residue of 1-methyl-4-carboxamidopyrrole-2-carboxylic acid or with a residue of analogue amino acids derived from an heterocycle different from pyrrole such as, without limiting the present invention, furan, imidazole, thiophene, thiazole, or derived from benzene, pyridine, a diazine, pyrimidine, substituted or not at the terminal amino group with an acylic group, or containing, in place of the free or substituted amino group a carboxamido group, and R_3 or R_4 are equal or

different lower alkyl groups C_1 to C_4,

the release system being a liposome, a micelle, a nanoparticle, a phospholipidic complex or in general terms a supramolecular phospholipidic structure able to incorporate a com pound of general structure **I** in stable and reversible form.

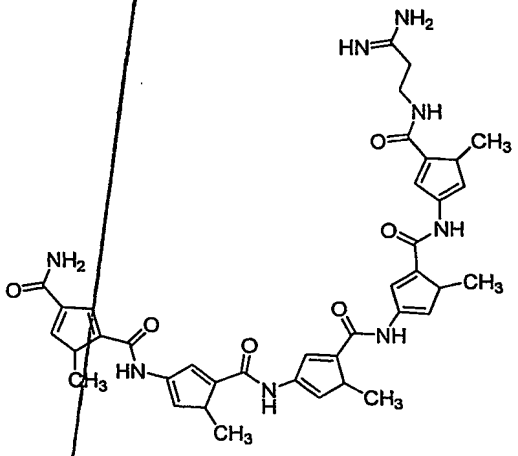
2. A phospholipidic preparation, consisting in a release system and of distamycin (**II**) in the form of an organic or inorganic salt, preferably as the hydrochloride,



II

in which the release system is a liposome, a micelle, a nanoparticle, a phospholipidic complex or in general terms a supramolecular phospholipidic structure able to incorporate **II** in stable and reversible form.

3. A phospholipidic preparation, consisting of a release system and of compound **X** in the form of an organic or inorganic salt, preferably as the hydrochloride,



X

in which the release system is a liposome, a micelle, a nanoparticle, a

phospholipidic complex or in general terms a supramolecular phospholipidic structure able to incorporate **X** in stable and reversible form.

4. A topical formulation based on a lexitropsin preparation as in claim 1, containing from 0.1 to 10% of active principle of general formula **I**, for the treatment of local microbial, viral or protozoan infections and for the treatment of localized tumours.

5. An injectable formulation, based on a lexitropsin preparation as in claim 1, for the medical treatment by a parenteral route, preferably by the intravenous, intramuscular, subcutaneous route, of generalized microbial, viral, protozoan infections or of disseminated tumours, at dosages comprised from 0.1 to 20 mg of a lexitropsin of general formula **I** per kg body weight.

6. A topical formulation based on a lexitropsin preparation as in claim 2 containing from 0.1 to 10% of active principle of general formula **II**, for the treatment of local microbial, viral or protozoan infections and for the treatment of localized tumours.

7. An injectable formulation, based on a lexitropsin preparation as in claim 2, for the medical treatment by a parenteral route, preferably by the intravenous, intramuscular or subcutaneous route, of generalized microbial, viral, protozoan infections or of disseminated tumours, at dosages comprised from 0.1 to 20 mg of a lexitropsin of general formula **II** per kg body weight.

8. A topical formulation based on a lexitropsin preparation as in claim 3 containing from 0.1 to 10% of active principle of general formula **X**, for the treatment of local microbial, viral or protozoan infections and for the treatment of localized tumours.

9. An injectable formulation, based on a lexitropsin preparation as in claim 3, for the medical treatment by a parenteral route, preferably by the intravenous, intramuscular or subcutaneous route, of generalized microbial, viral, protozoarian infections or of disseminated tumours, at dosages

comprised from 0.1 to 20 mg of a lexitropsin of general formula **X** per kg body weight.